SYNTHETIC ORGANIC CHEMICALS

PUBLISHED BY

Eastman Kodak Company, Rochester 4, N. Y.

VOLUME 19 • 1947 • NUMBER 2

Boron Fluoride Catalysis of Organic Reactions*

By J. ELMORE JONES**

(*Continued from Volume 19, Number 1*)

III. Reactions of Aromatic Compounds

A. NUCLEAR ALKYLATION.

The alkylation of aromatic hydrocarbons with olefins in the presence of boron fluoride and especially its complexes with water, organic acids, and sulfuric acid has been quite successful. Polyalkylation often takes place, just as with aluminum chloride, but boron fluoride *does not promote the migration of alkyl groups*. The rate of reaction has been shown to increase with the acidity of the compound with which boron fluoride is co-ordinated to produce the catalyst.

Aliphatic alcohols, with the exception of methanol and ethanol, are also useful alkylating agents. Early work led to the belief that the reaction involved olefin intermediates, since the ease with which the condensation takes place increases with the ease of dehydration of the alcohol (tertiary > secondary > primary), the addition of strong dehydrating agents (P_2O_5, H_2SO_4, $C_6H_5SO_3H$) increases the reaction velocity, and *n*-alcohols yield iso-alkyl derivatives. However, the alkylations with benzyl alcohol and the fact that optically active alcohols give optically active products formed a basis for Price's mechanism involving the polarization of the carbon-oxygen bond by complex formation and Burwell's alkyl-ion mechanism. On the basis of the experimental evidence, either of these may be the correct mechanism of the reaction.

Alkylations with alkyl halides, ethers, ethylene oxides and esters in the presence of boron fluoride catalysts have not been very successful. Among the alkyl halides, the tertiary group has produced the best yields.

The alkylation of a phenolic compound by an olefin may proceed by two different mechanisms; the conditions of reaction determine which is more prevalent. The olefin may be attached to the nucleus directly (as is the case with phenol ethers), or it may form a phenol ether which subsequently rearranges. By careful control of the conditions to minimize the rearrangement of the ether, it is possible to obtain a reasonably good yield of the phenol ether.

When alcohols are used for the alkylation, complex mixtures of the phenol, its ether, and various alkylation products and their ethers usually result. Methanol and ethanol do not alkylate phenols, but form only the O-ethers

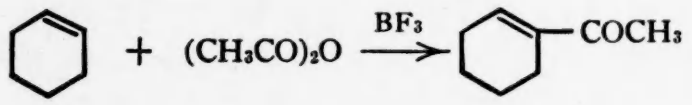
*This article is a condensation of a chapter on "Boron Fluoride as a Catalyst in Chemical Reactions" by D. Kastner in the book, "Newer Methods of Preparative Organic Chemistry," by Interscience Publishers, Inc., New York, 1947.

**Research Laboratories, Eastman Kodak Company, Rochester 4, N. Y.

which do not rearrange. Thus, in alkylations involving anisole, no rearrangement or cleavage of the methyl group takes place, but the ether undergoes nuclear alkylation. Complex mixtures of products resulting from nuclear alkylation, esterification and etherification are obtained by the action of propylene on the hydroxy benzoic acids.

B. INTRODUCTION OF NEGATIVE SUBSTITUENTS.

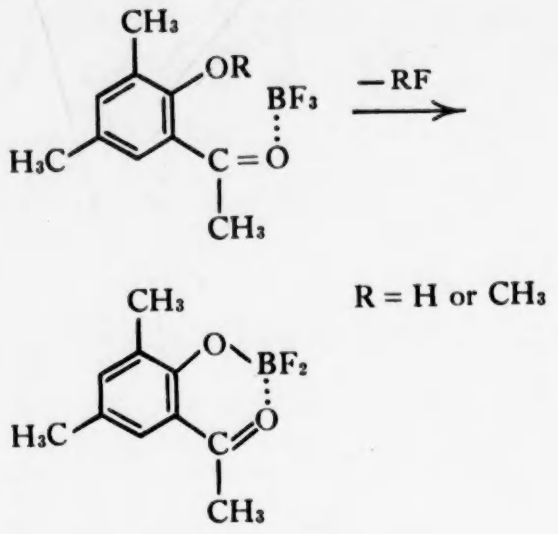
1. Acylation. Boron fluoride is not as effective as aluminum chloride in promoting condensations between benzene or toluene and acetic anhydride, but reactions between anisole and acetic anhydride or resorcinol and phthalic anhydride give good yields of *p*-methoxyacetophenone and fluorescein, respectively. Olefins such as cyclohexene also react with acetic anhydride to give α, β-unsaturated ketones,



but the autocondensation of acetic anhydride catalyzed by boron fluoride limits the usefulness of the reaction.

A preferable method for acylating phenols or their ethers consists in heating a solution of the phenolic compound in a fatty acid with boron fluoride in a sealed vessel at 70°C. for two hours. Good yields (80-90%) of the acylation products are obtained.

In those cases in which the acyl group enters the *meta* or *para* position to the hydroxyl group, the liberation of neither hydrogen fluoride nor fluoromethane has been detected. This is in direct contrast to aluminum chloride, which always liberates hydrogen chloride when used as a catalyst. In the case of *ortho* substitution, however, stable inner complexes result from the elimination of hydrogen fluoride between the *o*-hydroxy (methoxy) group and the boron fluoride complex of the acyl group.



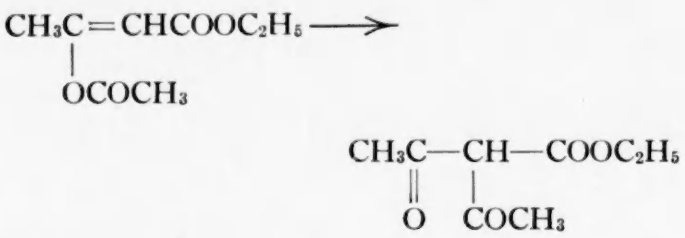
The acylation of phenols by means of organic acids is not necessarily a direct nuclear substitution, since there is evidence in favor of a mechanism involving the formation of a phenyl ester and its rearrangement. By interrupting the reaction between 2, 4-dimethylphenol and acetic acid before it is complete, a good yield of the phenyl acetate is obtained. Thus, a Fries rearrangement takes place during the reaction.

Although aluminum chloride is the usual catalyst for Fries rearrangements, boron fluoride has been employed advantageously in studies on the mechanism of the reaction. The boron fluoride complexes of the phenyl esters and ketones involved are soluble in organic solvents such as nitrobenzene, chlorobenzene, and boron fluoride-acetic acid, and crystallize well. Thus, the reaction may be studied in homogeneous media below 100°C. and well-defined products can be isolated. Not only does the rearrangement take place in solution as well as in the molten state, but it also proceeds in the crystals of the boron fluoride complexes.

The work with boron fluoride tends to favor the intramolecular mechanism proposed by Auwers and Mauss. An ester does not acylate another molecule of ester (although it will acylate a phenol or ether) under the conditions used, and kinetic studies have shown that the reaction of boron fluoride-phenyl acetate is unimolecular in solutions at 20°C.

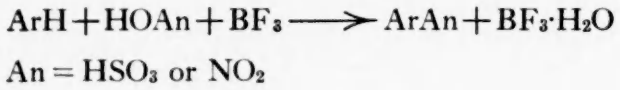
The rearrangements always produce *ortho* and *para* derivatives under mild conditions, so that the rearrangements reported in the literature where *meta* substitution appeared to take place were probably nuclear acylations.

The rearrangement of enol acetates by treatment with boron fluoride under mild conditions produces good yields of β-diketones. O-acetylacetoacetic ester gives the C-acetyl derivative in a yield of 94 per cent.



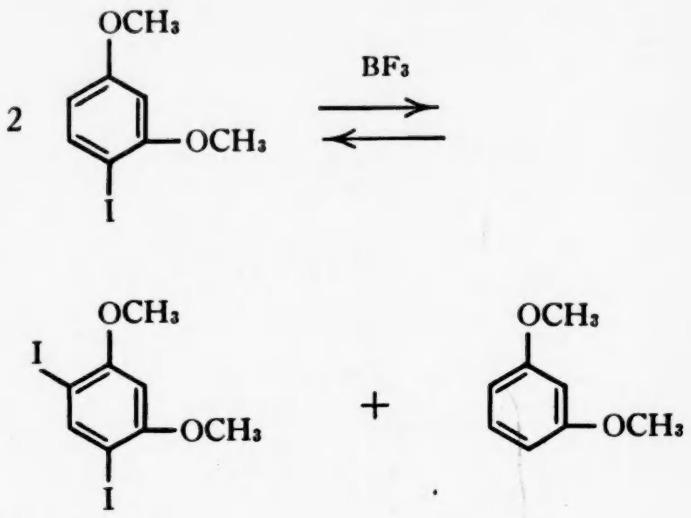
The rearrangement of cyclohexenyl acetate is less smooth.

2. Nitration and Sulfonation. Boron fluoride is particularly useful for the catalysis of the sulfonation and nitration of aromatic compounds. An excess of acid is unnecessary since the equilibrium is displaced by the removal of water as the hydrate of boron fluoride.

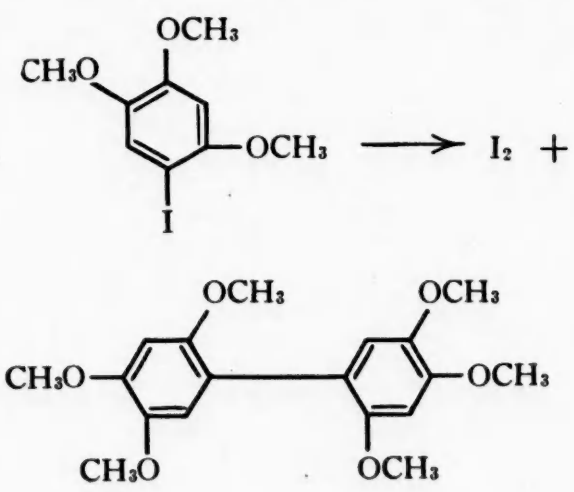


Other advantages to the use of boron fluoride are that the reactions proceed at lower average temperatures (40°-100°C.) and at greater rates than usual, so that better yields of products of higher purity are obtained. Boron fluoride does not accelerate the sulfonation of all aromatic compounds (such as chlorobenzene, nitrobenzene, benzoic acid), but it is particularly useful for the nitration of compounds containing such negative groups. The nitration of nitrobenzene and benzoic acid gives good yields of *m*-dinitrobenzene (87%) and *m*-nitrobenzoic acid (82%). In cases in which a nitration reaction is to follow a sulfonation, the intermediate sulfonic acid need not be isolated, but nitric acid and fresh boron fluoride may be added to convert the sulfonic acid to a nitrosulfonic acid. *m*-Nitrobenzenesulfonic acid has been prepared in 80 per cent yield by this method.

3. Halogen Shifts. The interesting rearrangement of the iodine atom in iodoresorcinol dimethyl ether was originally carried out in the presence of boron fluoride before the discovery that other catalysts, such as stannic and aluminum chlorides and mineral acids, would effect it.



Although an equilibrium reaction is involved, it goes to completion (90%) in ether solution, since the diiodo compound is insoluble. The mechanism is an intermolecular one in which the iodine atom is liberated by the polarization of the carbon-iodine bond by the boron fluoride complex of the ether linkage; thus, one molecule iodinates another. In accord with this hypothesis, bromides and chlorides require much higher temperatures for rearrangement. If the 6-position is occupied, the reaction leads to coupling and iodine is liberated.



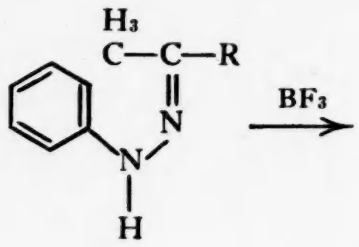
4. Preparation of Fluorides. Another reaction of interest involving boron fluoride, which was the first useful one for the synthesis of fluorobenzene, is the decomposition of diazonium borofluorides.

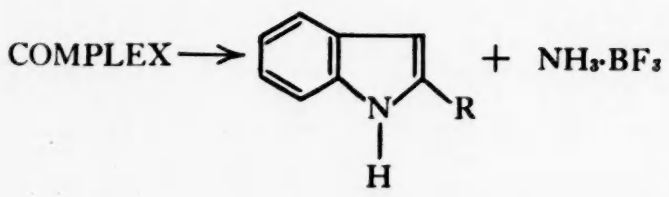
$$C_6H_5N_2BF_4 \xrightarrow{\text{heat}} C_6H_5F + N_2 + BF_3$$

The diazonium salt is usually decomposed by pyrolyzing a mixture of it and an inert substance either at atmospheric pressure or *in vacuo*. The reaction has been applied quite generally but the yields are often not satisfactory. The solubilities of the diazonium borofluorides as well as their behavior on thermal decomposition are limiting factors.

C. THE FISCHER INDOLE SYNTHESIS.

With few exceptions, the use of boron fluoride for the catalysis of Fischer indole syntheses has resulted in yields comparable to those obtained by other agents. Boron fluoride is quite superior to other catalysts, inasmuch as the products can be isolated and purified more easily. It forms complexes with the phenylhydrazones which are decomposed most conveniently in acetic acid solution.





One of three methods is generally used:

(1) A solution of the phenylhydrazone which has been saturated with boron fluoride is refluxed;

(2) Boron fluoride is bubbled through a refluxing solution of the hydrazone;

(3) Boron fluoride etherate is added to the phenylhydrazone, the ether is evaporated, and the residual solid is heated to 100-130°C., or is dissolved in acetic acid and refluxed.

The last method, which is considered the best, takes advantage of the fact that phenylhydrazones, being stronger bases than ether, will displace boron fluoride from its ether complex; this makes accurate measurement of the amount of catalyst possible. The use of boron fluoride has not resulted in the condensation of any phenylhydrazones which have not been converted to indoles by other catalysts.

IV. Condensations Involving Reactive Hydrogen Atoms

A β-diketone is obtained simply by saturating a cold mixture of a ketone and acetic anhydride with boron fluoride. Similarly, esters give β-keto esters, and anhydrides of aliphatic acids condense with themselves to yield anhydrides of β-keto acids. The autocondensation of the anhydrides and the fact that unsymmetrical ketones are acylated on both sides of the keto group limits the usefulness of the reaction, but in certain cases the yields are good and little or no isomeric material is formed.

$$C_6H_5COCH_3 \xrightarrow{83\%} C_6H_5COCH_2COCH_3$$

$$CH_3COCH_2CH_3 \longrightarrow CH_3COCHCOCH_3 \text{ (exclusively)}$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\quad CH_3$$

When acylation is possible on both sides of the keto group, increasing substitution on the β-carbon atom lowers the percentage of acylation on that side. Unsaturated ketones condense also, but their polymerization is a complicating factor.

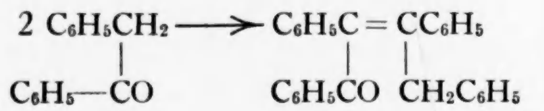
The autocondensation of acetic anhydride gives an excellent yield (90%) merely by saturating the anhydride (cooled in an ice-salt bath) by boron fluoride. The product, which crystallizes from the solution as the boron fluoride complex, is the anhydride of diacetyl-

acetic acid; its hydrolysis yields acetyl acetone by decarboxylation of the acid.

$$(CH_3CO)_2O \longrightarrow [(CH_3CO)_2CHCO]_2O \xrightarrow{H_2O} (CH_3CO)_2CHCOOH \longrightarrow (CH_3CO)_2CH_2$$

The higher anhydrides give predominantly the monoacyl derivatives, and in those cases a monoketone is obtained on hydrolysis. No crystalline complexes are formed in those cases except in that of iso-butyric anhydride.

Not all ketones undergo acylation, since some have such reactive methylene groups that other condensations may take preference. Thus, desoxybenzoin condenses with itself.



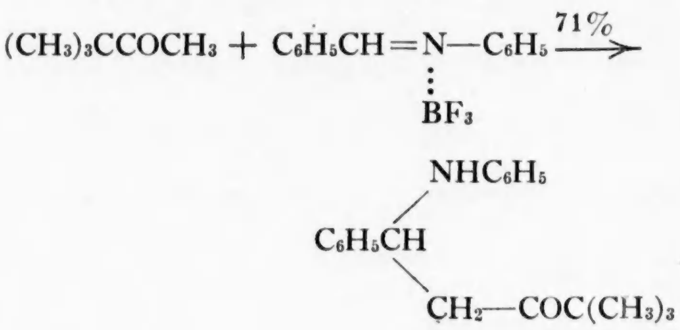
A number of reactions of active hydrogen atoms which normally are carried out in basic media have been effected by Hauser with boron fluoride catalysts. Examples of these are the following:

$$C_6H_5CHO + CH_3COC_6H_5 \xrightarrow{61\%} C_6H_5CH = CHCOC_6H_5$$

$$C_6H_5CHO + H_2C(COOC_2H_5)_2 \xrightarrow{58\%} C_6H_5CH[CH(COOC_2H_5)_2]_2$$

Attempts to use boron fluoride in the Perkin reaction have not been very successful.

Snyder utilized the boron fluoride-catalyzed additions of compounds with reactive hydrogen atoms to benzalaniline for the production of β-aminoketones in yields varying from 30 to 70 per cent. Certain hindered ketones, such as acetomesitylene, failed to react.



V. The Cleavage of Ethers

The cleavage of aliphatic ethers by acid chlorides or anhydrides, which takes place rather easily in the presence of various anhydrous metal chlorides, such as those of aluminum or zinc, can be effected by boron fluoride also. The cleavage products, depending upon the reagent used, are one mole each of an alkyl halide and an ester, or two moles of an ester. Boron fluoride has been of particular value in studies on the mechanism of the reaction.

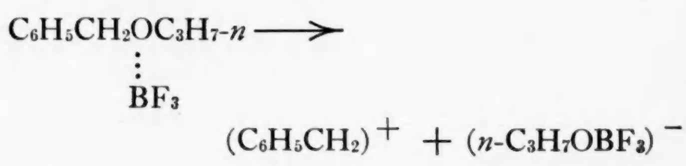
The reaction involving acid chlorides does not proceed as smoothly with boron fluoride as it does with the more common catalysts, but the cleavage with anhydrides gives better results.

$$ROR + (R'CO)_2O \xrightarrow{BF_3} 2\ ROCOR'$$

Although the reaction does take place at room temperature, higher temperatures (100-200°C.) are often necessary to cause it to proceed at a reasonable rate.

The amount of catalyst necessary depends upon the stability of the boron fluoride complexes of the products. If these complexes are more stable than those of the starting materials, the boron fluoride is removed from the reaction as it proceeds and one mole of catalyst is needed for each mole of ether cleaved. Otherwise, only catalytic quantities are necessary.

In a study of the cleavage of benzyl *n*-propyl ether, Hennion came to the conclusion that the ether splits to form a benzyl cation and a propoxy-boron fluoride anion.



Each fragment reacts in a specific way, since in a mixture of acetic acid and benzene, the products obtained were *n*-propyl acetate and diphenylmethane (benzylbenzene).

New Eastman Organic Chemicals

5625	γ-Bromobutyronitrile BP 100-101°/20 mm.	10 g. ..	$1.75	B
	$BrCH_2CH_2CH_2CN$ . . . MW 148.01			
4177	n-Butyl Crotonate BP 178-180°	1 kg...	5.00	E
	$CH_3CH{:}CHCOO(CH_2)_3CH_3$ . . . MW 142.19			
T 5770	n-Butylphosphoric Acid (Techn.)	1 kg...	2.55	E
P 3424	1,3-Diaminopropanol-2 (Pract.) MP 15-25°	1 kg...	5.00	E
	$(NH_2CH_2)_2CHOH$ . . . MW 90.13			
T 5778	1,3-Dichloro-2-butene (Techn.)			
	88% boiling at 125-131°	3 kg...	7.65	G
	$ClCH_2CH{:}CClCH_3$ . . . MW 125.00			
T 5764	Ethylphosphoric Acid (Techn.)	1 kg...	2.35	E
T 4435	Glyoxal (30% in water) (Techn.)	3 kg...	4.50	G
	CHOCHO . . . MW 58.04			
5769	9-Heptadecanone MP 49-51°	100 g. ..	6.00	C
	$[CH_3(CH_2)_7]_2CO$ . . . MW 250.41			
T 5759	4-(β-Hydroxyethyl)pyridine (Techn.)			
	75% boiling at 158-161°/18 mm.	100 g. ..	2.00	C
	$CH{:}CHN{:}CHCH{:}CCH_2CH_2OH$ . . . MW 123.15			
5744	Methyl Bicyclo[2,2,1]5-heptene-2,3-dicarboxylate			
	MP 35-37°	100 g. ..	6.00	C
	$CH_2CHCH{:}CHCHCHCH(COOCH_3)_2$ . . . MW 210.22			
P 5750	Methyl Crotonate (Pract.) 90% boiling at 117-119°	1 kg...	8.00	E
	$CH_3CH{:}CHCOOCH_3$ . . . MW 100.11			
T 5760	Methylphosphoric Acid (Techn.)	1 kg...	2.55	E
5780	5-Nitrofurfural Diacetate MP 90-92°	10 g. ..	2.00	B
	$OCNO_2{:}CHCH{:}CCH(OCOCH_3)_2$ . . . MW 243.17			
5768	8-Pentadecanone MP 37-39°	100 g. ..	6.00	C
	$[CH_3(CH_2)_6]_2CO$ . . . MW 226.39			
T 5766	n-Propylphosphoric Acid (Techn.)	1 kg...	2.55	E
T 5753	4-Sulfophthalic Anhydride (90%) (Techn.)	1 kg...	2.95	E
	$HOSO_2C_6H_3$-1,2-$(CO)_2O$ . . . MW 228.17			
5743	cis-$\triangle^4$-Tetrahydrophthalic Acid MP 171-173°	100 g. ..	6.00	C
	C_6H_{10}-1,2-$(COOH)_2$ . . . MW 172.18			
2753	Tetraphenyltin MP 227-229°	100 g. ..	4.50	C
	$(C_6H_5)_4Sn$ . . . MW 427.10			